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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brian Seed et al.	Art Unit:	1644
Serial No.:	09/243,008	Examiner:	Patrick J. Nolan
Filed:	February 2, 1999	Customer No.:	21559
Title:	REDIRECTION OF CELLULAR IMMUNITY BY RECEPTOR CHIMERAS		

Mail Stop Appeal
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' REPLY BRIEF
SUBMITTED PURSUANT TO 37 C.F.R. § 1.193

In response to the Examiner's Answer mailed on July 1, 2003, Appellants submit, in triplicate, the following Reply Brief.

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Status of Claims

Following the Examiner's Answer, claims 44-47, 51-52, 56-57, 60-64, 66, 68, 70, 72-75, 77, 79-82, and 92-101 are pending. Claims 1-43, 48-50, 53-55, 58, 59, 65, 67, 69, 71, 76, 78, and 83-91 have been canceled. Claims 56-57, 60-64, 66, 68, 70, 77, 80-82, and 92-99 stand withdrawn from consideration. Claims 44-47, 51, 52, 72-75, 79, 100, and 101 were finally rejected in a Final Office Action mailed on July 3, 2002 and are appealed.

Status of Amendments

All amendments have been entered.

Grouping of Claims

The claims stand or fall together.

Argument

The pending claims stand rejected based on an assertion of a lack of written description. Appellants' response to this rejection and the issues raised by the Office in the Examiner's Answer are presented below.

The Written Description Rejection Should be Reversed

Appellants' invention features cells expressing a combination of immune cell chimeric receptors and CD28 chimeric receptors. Such receptors direct the recognition and destruction of specific targets, e.g., pathogens or cells infected with pathogenic agents such as HIV. This invention is claimed in independent claims 44 and 79, as well as their dependent claims.

Claim 44, as filed, was directed to a cell which expresses at least two proteinaceous membrane-bound chimeric receptors, the first receptor including an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor capable of signaling the cell to destroy a receptor-bound target cell or a receptor-bound target infective agent. The second receptor includes an extracellular portion which is capable of specifically recognizing and binding the target cell or target infective agent and an intracellular portion which is derived from CD28.

Claim 79, as filed, was also directed to a cell which expresses at least two proteinaceous membrane-bound receptors, the first of these receptors including an extracellular portion which is capable of recognizing and binding a target cell or target infective agent, and a transmembrane portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor. In claim 79, the second receptor again included an extracellular portion capable of specifically recognizing and binding the target cell or target infective agent and an intracellular portion derived from CD28.

In response to the first Office Action, Appellants amended claim 44 to emphasize that the transmembrane domain was responsible for signaling by adding the phrase "in the absence of an intracellular signalling domain" to part (b). To further highlight this point, Appellants also added, to claims 44 and 79, part (c) which recites that the receptor includes "an intracellular domain that does not signal said cell to destroy said receptor-bound target cell or receptor-bound target infective agent." As was noted in Appellants' reply and Appeal Brief, these amendments were fully supported by the original specification, for example, at page 48 and by Figures 8A and 8B, where a chimeric receptor having a transmembrane signaling domain is shown and demonstrated to direct its host cell to destroy a receptor-bound target.

In the Examiner's Answer, the Office continues to assert (page 3):

> Applicant has no support in the originally filed claims or specification for the genus phrase language 'an intracellular domain that does not signal to said cell to destroy a receptor-bound target cell or receptor-bound target infective agent.'

In addition, the Office questions (page 4):

> How does this one species support the sub genus claim of all chimeric receptors with an extracellular domain, an intracellular [*sic*; a transmembrane] domain that signals a cell to destroy a receptor bound target cell and wherein said cell further comprises any and all intracellular domains that does not signal said cell to destroy a receptor-bound target cell?

Appellants address these issues as they relate to the legal standard for written description as follows.

I. Legal Standard

To satisfy the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of the invention. The Federal Circuit has held that the specification does not need to precisely describe all subject matter that is claimed. *In re Daniels*, 114 F.3d 1452, 46 U.S.P.Q.2d 1788 (Fed. Cir. 1998); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 U.S.P.Q. 177 (Fed. Cir. 1985). As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

> [T]he specification must 'convey clearly to those skilled in the art to whom it is addressed ... the information that [the inventor] has invented the specific subject matter later claimed.'

Moreover, the M.P.E.P. (§ 2163.02; Eighth Edition, August 2001) states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she has invented what is claimed."

In applying this standard, the Federal Circuit has held that the specification must convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). As set forth below, Appellants' specification meets this standard for the presently claimed invention.

II. Original Claim 44 Was Directed to a Chimeric Receptor Having a Transmembrane Signaling Domain

Original claim 44 recites "a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or a receptor-bound target infective agent" (emphasis added). The amendments made to claims 44 and 79 during the prosecution of the application do no more than highlight the fact that it is the transmembrane domain that signals, and that the intracellular domain does not signal the cell to destroy a receptor-bound target cell or receptor-bound target infective agent.

The Examiner's Answer addresses this amendment as follows (page 5):

> Appellant amended the claim by insertion of the third part of the chimeric receptor, an intracellular domain, which Appellant clearly has support for in their originally filed specification, but said intracellular domain is required to not signal the destruction of the host. This property of such an intracellular domain is contrary to most tenets of T cell activation, since activation of T cells is accepted by those of skill in the art to occur via the intracellular domain.

This basis for the written description rejection is unavailing. First, whether or not the claimed property of the intracellular domain is "contrary to most tenets of T cell activation" is largely irrelevant to the issue of written description. Moreover, Appellants' discovery that a transmembrane domain can signal target cell destruction represents an important finding in understanding receptor function and was subsequently published in the scientific literature (e.g., Romeo et al., "Sequence Requirements for Induction of

Cytolysis by the T Cell Antigen/Fc Receptor ζ Chain" Cell 68:889-897, 1992; and Romeo et al., "Activation of Immune System Effector Function by T-Cell or Fc Receptor Intracellular Domains" Cold Spring Harbor Symposia on Quantitative Biology 57:117-125, 1992; both of these references were cited on the Information Disclosure Statement filed on April 27, 1999).

In short, what is important here to the issue of written description is the fact that Appellants, in their specification and in originally filed claim 44, described and claimed chimeric receptors having a transmembrane domain capable of signaling target destruction. On this basis alone, the rejection should be reversed.

III. Appellants' Specification Includes a Working Example of a Chimeric Receptor Having a Transmembrane Signaling Domain

In further support for Appellants' satisfaction of the written description requirement, the Office has been directed to page 48 of the specification and to Figures 8A and 8B, where Appellants provide a working example of a chimeric receptor having a transmembrane signaling domain. In response, in the Examiner's Answer, the Office asserts (page 3, page 5, page 7):

> Applicant argues they have support for the claimed invention on page 48, lines 31-33, where they describe a chimera which has a full length extracellular domain, a full length transmembrane domain and a 3 amino acid intracellular domain ... From this disclosure, Applicant's representative has concluded completely without any direct evidence that the first chimera that had only three amino acids intracellularly was only working as a 'nub' to anchor the chimera into the

> membrane and did not by her assertion act as a signal transmitter.
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> * * *
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> In fact, to support their claim the one example of an intracellular domain that did not transmit a signal to destroy the receptor bound target cell, appellant supplied a declaration [in] support of said fact, since the specification had no *ipsis verbis* support for such a recitation and the Appellant's argument of inherency could only be established by an evidentiary showing, by one of skill in the art.
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> * * *
>
> At no point did they disclose that the chimeric receptors were not signaling destruction of the target cell via the intracellular domain, only that the transmembrane domain was capable. The amendment of the claimed invention to include an intracellular domain that does not signal a cell to destroy a target cell was only established in one working example via a declaration after the original filing for one species.[1]

Again, the Office's position regarding Appellants' specification is in error. As noted above, Appellants' specification has from its original filing date described and claimed chimeric receptors that signal through their transmembrane domains. For example, at page 48, lines 20-33, a number of chimeras having intracellular domains of reduced length are described. One such chimera, disclosed at lines 31-33 and in Figure 8A, possesses a transmembrane domain joined to an intracellular domain of only three amino acid residues (amino acids 31-33; RVK). In describing the chimera, the

[1] The Office also states (page 7): Whether it would have been obvious to one of skill in the art that by creating a chimeric receptor that transmits a signal to destroy a target cell via the transmembrane domain would allow one to conclude that the same chimeric receptor is not at the same time doing so via its intracellular domain is not the legal standard for written description.

specification states (page 48, lines 31-33):

> [C]omplete loss of activity was not observed even when the intracellular domain was reduced to a three residue transmembrane anchor. (emphasis added)

Clearly, this chimeric receptor is capable of signaling and does so through its transmembrane domain, its intracellular domain merely anchoring the chimera in the cell membrane.

Appellants were well aware that this three amino acid anchor did not signal, as it was conclusively proven by other experiments described in the specification. For example, at page 51, lines 18-19, the specification describes chimeric receptors in which an amino acid important for signaling, the tyrosine residue at position 62, was converted to either phenylalanine or serine. Constructs expressing these receptors, which included amino acids 31-33 of the intracellular domain, did not signal target destruction. Thus, this three amino acid intracellular portion cannot on its own act as a signaling domain, and, contrary to the Office's assertion, Appellants' arguments are supported by the specification as filed, in no way requiring an independent evidentiary showing by one skilled in the art.

In fact, the Declaration by inventor Dr. Brian Seed, submitted with Appellants' reply to the Office Action mailed on October 23, 2001, simply highlights the teachings of the specification. In particular, Dr. Seed attests to the fact that intracellular amino acids 31-33 (RVK) do not signal, but rather anchor the chimera in the cell membrane. Dr. Seed also states that his data presented in the specification indicate that signaling by this

chimeric receptor is mediated by the transmembrane domain, precisely as claimed in the original and instant claims.

Thus, contrary to the Office's position, "direct evidence" has been presented in Appellants' specification for a chimeric receptor having a transmembrane receptor domain that signals. "Direct evidence" has also been presented for intracellular receptor domains that do not signal. And "direct evidence" has been presented for the fact, specifically, that intracellular amino acids 31-33 (RVK) do not signal. It is without possible dispute therefore that Appellants describe in their specification a chimeric receptor that transmits a signal through its transmembrane, rather than its intracellular, domain. It is this aspect of Appellants' invention that is conveyed by claim 44, now and as originally filed. No sub-genus has been created (as asserted by the Office), and Appellants for this reason as well point out that the Office's position is in error and should be reversed.

Finally, in the Examiner's Answer, the Office further asserts (page 6):

> Lastly, Appellant's own specification discloses on page 50, lines, 5-10, that it was most likely by association with other chains that cytolytic activity of the activated cell was maintained. In other words Appellants first receptor was transmitting destruction of the target cell by associating with a full length chimera, that had a fully functioning intracellular domain.

Once more, the Office relies on statements unrelated to written description. The claimed chimeric receptors (and those referred to by the Office) signal through a transmembrane domain and have an intracellular domain that does not signal target destruction. The

chimeric receptors referred to by the Office exemplify the claimed invention, and whether or not they signal by associating with another receptor is irrelevant. A written description for the cell carrying this type of receptor does not rely on an understanding or description of its mechanism of action. In fact, the teachings relied upon by the Office no more than provide further support for the present claims in the original specification.

IV. The Written Description Rejection Has Been Satisfied in the Present Application

Appellants submit that, to fulfill the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. The Federal Circuit has held that the specification does not need to describe exactly all the subject matter that is claimed. *In re Daniels*, 114 F.3d 1452, 46 U.S.P.Q.2d 1788 (Fed. Cir. 1998); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 U.S.P.Q. 177 (Fed. Cir. 1985). As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

> [T]he specification must 'convey clearly to those skilled in the art to whom it is addressed ... the information that [the inventor] has invented the specific subject matter later claimed.'

To satisfy this standard, the Federal Circuit has held that the specification need only convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).

Appellants' specification plainly meets the written description standard by providing a working example of a chimeric receptor that signals through a transmembrane, rather than an intracellular, domain. This description, which is beyond dispute, would be recognized by one skilled in the art. Moreover, Appellants have, from the time they originally filed this application, claimed this type of transmembrane-signaling receptor as part of their invention. One skilled in the art therefore certainly would recognize that, at the time of filing, the inventors were in possession of chimeric receptors that signal through transmembrane (rather than intracellular) domains. The written description requirement of § 112, first paragraph has been satisfied by Appellants, and the rejection of claims 44-47, 51, 52, 72-75, 79, 100, and 101 under § 112, first paragraph, should be reversed.

Conclusion

Appellants respectfully request that the rejection of claims 44-47, 51, 52, 72-75, 79, 100, and 101 be reversed.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 14 August 2003

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